

Adding Value to Routine Oral Bioavailability Studies

Dr Paul J Clewlow, Business Development Director

Pharmaceutical Profiles, Mere Way, Ruddington, Nottingham, NG11 6JS, UK

Introduction

From 1970 to 2001, the R&D expenditure of the global pharmaceutical industry increased from 11.4% of sales to 18.5% of sales. It is anticipated that pharmaceutical R&D spending will continue to expand at a rate of more than 12% *per annum* for the foreseeable future. More than 75% of the cost of producing new drugs has been attributed to previous development failures (Wilding, 2002) – a frightening statistic for an industry that prides itself on being innovative and ‘cutting edge’.

Another key driver of this growth in R&D expenditure is the increasing threat faced by large pharmaceutical companies from their generic competitors. According to **Ernst & Young**, US\$100 B of products face patent expiry by 2004 (Wilding, 2002). By 2005, patents will have expired on 17 of today's 20 top marketed drugs. Over the next few years, the top ten pharmaceutical companies will face, on average, a 32% exposure of their sales to generic competition.

It will be difficult for most pharmaceutical companies to gain more than half of their future growth requirements from products currently on the market. Consequently, this will place a heavy burden on the new molecular entities (NMEs) in development to fuel future incremental sales growth. Leading pharmaceutical companies are predicting a 65% increase in the number of NMEs entering development by 2008 and estimate the success rate in bringing these to the market will have to treble over the same period to achieve the forecast growth targets. However, **Lehmann Brothers** estimates that the average cost of bringing a new drug to market could soar to US\$1.6 B by 2005 (Wilding, 2002).

The advent of proteomics, genomics, combinational chemistry and high-throughput screening has given rise to an unprecedented number of drug candidates that are more complex than those previously developed using traditional methodologies. The current discovery effort is producing molecules with improved pharmacology, but less than perfect oral delivery (biopharmaceutical) properties. It is increasingly recognised that NMEs must exhibit desirable biopharmaceutical properties, as well as the necessary efficacy indicators to warrant selection as lead clinical candidates. This recognition has been fuelled by the advent of the Biopharmaceutical Classification System (BCS). This System is now widely used to categorise the oral absorption properties of drugs according to their solubility and permeability (Wilding, 1999). It has been embraced by regulatory authorities worldwide, most notably the US **FDA**, and has been incorporated into a number of regulatory guidelines.

The pharmaceutical companies that will be successful in the current highly-competitive environment are those that are best able to determine, from an early stage, which of their drug candidates are the most likely to pass the compulsory regulatory and efficacy hurdles to become approved medications. It is widely acknowledged that a major factor in boosting success rates will be better characterisation of compounds at the pre-clinical/early clinical phase interface; with improved candidate selection being based on a much better understanding of biopharmaceutical properties, scalability of manufacture and toxicology. Significant amounts of time, money and resources can be wasted on developing the wrong compounds if the relevant clinical data is not available early in development to make truly informed decisions.

Early Clinical Development – the Key to Future Success

Early phase drug development clinical studies (Phase I trials) are generally carried out in small numbers of healthy volunteers and are used to provide an initial evaluation of a drug's safety and pharmacokinetic profile (absorption, distribution, metabolism and excretion). Frequently, such Phase I studies are used to evaluate a range of doses of a drug to obtain an indication of the appropriate dose for use in later phase clinical studies.

Bioavailability studies are essential to drug development and form an integral part of the registration dossier. To formally characterise and assess the pharmacokinetic performance of almost every oral product, worldwide regulatory authorities demand that a range of clinical studies are undertaken in healthy volunteers. Such studies typically take place throughout the development cycle of a drug, ranging from early single dose rising studies and absolute oral bioavailability investigations, through to steady state and food effect studies and finally to the evaluation of specific drug–drug interactions.

Results from these pharmacokinetic studies ultimately affect how the product is prescribed and so dictate its safe and effective use in patients. However, these routine bioavailability studies by no means provide a complete picture of a drug's biopharmaceutical properties. Today, many of the compounds exiting drug discovery and embarking on the difficult road of product development have highly complex biopharmaceutical properties. The secret to successful and cost-effective product development is collecting as much information as possible from standard bioavailability studies undertaken in healthy volunteers en route to regulatory filing. Much of the cost of undertaking a human pharmacokinetic-only study is ‘fixed’ and

essentially independent of the size and complexity of the study design. Consequently, significant 'added value' can be achieved by designing studies that will answer multiple questions, rather than just one simple question.

Precision Drug Delivery within the GI Tract

Until recently, there has only been a limited understanding of what actually controls human drug absorption. New techniques for assessing the factors influencing drug absorption from different regions of the gastrointestinal (GI) tract have gone some way to addressing this key question. Increasingly, pharmaceutical and drug delivery companies are undertaking regional absorption studies during early clinical development to provide more reliable 'route maps' for developing new drugs with complex pharmacokinetic properties. These absorption studies provide the means to generate radical innovations in product development because they provide mechanisms for making informed decisions around the bioavailability of a candidate drug.

To promote a more proactive approach to oral drug development, **Pharmaceutical Profiles** has recently launched an innovative new early phase clinical development service called *PKPlus*. This service combines standard Phase I bioavailability studies with Pharmaceutical Profiles' unparalleled experience and expertise in the arena of regional drug absorption studies utilising the proprietary Enterion™ capsule (Wilding *et al.*, 2000) (Figure 1). Enterion™, developed by **Phaeton Research** (Nottingham, UK), is the latest advance in the arena of remote controlled, engineering-based drug delivery capsule technologies, designed to overcome the limitations of earlier devices (Houzeo *et al.*, 2001a, b). It has been specifically engineered to target the delivery of candidate drugs to specific regions of the human GI tract. Housed within the round-ended capsule body (32 mm x 11 mm) is a 1 cm³ drug reservoir that can be filled with the drug substance or formulation in almost any physical form (fine powder, granulate, pellets, semi-solid gel, suspension or solution).

Prior to oral administration, a small amount of a non-released gamma ray-emitting radionuclide is incorporated

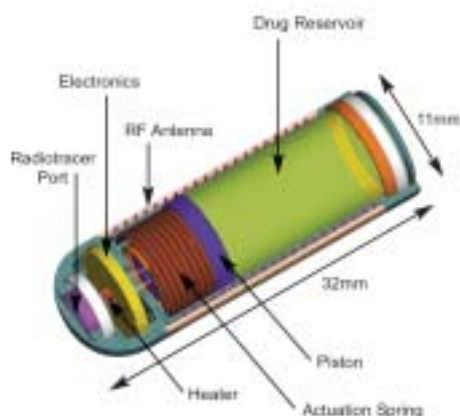


Figure 1 – The Enterion™ capsule.

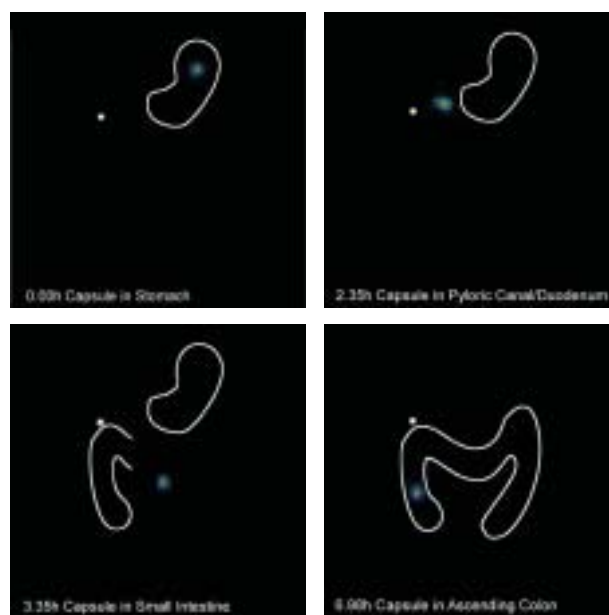


Figure 2 – Scintigraphic images of the Enterion™ capsule transiting through the GI tract.

into a separate compartment at the tip of the capsule. Once swallowed, the transit of the capsule from the stomach and along the intestinal tract is tracked in real-time using gamma scintigraphy (Figure 2). On reaching the intestinal site of interest, an external radio-frequency generator is used to produce an electromagnetic field around the subject's abdomen for a few seconds. A receiving coil embedded around the capsule wall picks up this field, causing induction of a tiny electric current. This electric current operates a novel latch mechanism, releasing a spring-driven piston that actively expels the capsule contents into the gut lumen in a rapid, bolus fashion. Following successful activation of the capsule, a radio signal is transmitted back to the radio-frequency generator.

Extra Help in Understanding Regional Drug Absorption

Using the Enterion™ capsule, incorporated into a crossover clinical study design, it is possible to determine the absorption of a drug throughout the human gastrointestinal tract. The absorption data generated can be pivotal to understanding the biopharmaceutical properties of a new molecular entity and what factors might limit its oral bioavailability (Wilding, 2001). These data can guide the pharmaceutical scientist towards the most effective drug delivery approach for a specific compound (Connor *et al.*, 2001; Wilding *et al.*, 2003).

Bioavailability properties determine a drug's likely concentration in the blood stream and at receptor sites. If these properties are wrong, there is a strong chance of unwanted side effects or limited efficacy – even when the compound has the optimal chemistry for interaction with the drug target. Two properties well known to influence bioavailability are *in vivo* solubility and permeability across the intestinal epithelium. Since both will inevitably vary along the heterogeneous environment of the GI tract, standard laboratory measurements, such as the drug's pH-

dependent solubility profile and permeability across Caco-2 cells only provide an indication to which of these two primary factors is most likely to limit oral bioavailability.

A far more reliable method to determine a drug's oral bioavailability is to directly compare the absorption of a particulate form of the drug *versus* a solution (or solubility enhanced) form, when the drug is specifically targeted to intestinal regions of interest, such as the distal small bowel or ascending colon. If the solution form of the drug shows a higher extent of absorption over the particulate form, then bioavailability is almost certainly limited by solubility. However, if the regional absorptions of the two dosage forms are comparable, then bioavailability is permeability limited.

Of course, solubility and permeability are not the only biopharmaceutical properties of interest. The influence of gut-wall (CYP3A4 mediated) metabolism and intestinal efflux systems (such as P-gp transporters) apply to many classes of drug (Wilding, 1999). However, the *in vivo* mechanisms are less well-understood and actual effects harder to predict from pre-clinical models. Such processes are clearly difficult to study during conventional human PK studies, especially with high inter-subject variability typical of enzyme expression. However, drugs suspected as substrates can be purposely evaluated using the Enterion™ capsule. For example, inhibitors of the suspected enzyme systems can be pre- or co-targeted to the same intestinal region as the test drug. This will not only confirm if the drug is a substrate, but also the extent to which bioavailability is affected in a particular segment of the GI tract.

Extra Data, Early On – When it's Needed

During the early stages of product development, future drug delivery requirements are usually unknown - either for the lead dosage form or for subsequent life-cycle management opportunities. Undoubtedly however, the increasing complexity of clinical candidates is demanding the development of ever-more sophisticated oral drug delivery systems. It is the drugs with complex PK properties that could benefit the most from introducing regional absorption study arms into standard bioavailability studies because they will eventually need one or more of the following technologies to stay in oral development:

- Sustained or extended release
- Pulsed release or another type of chronotherapeutic delivery technology
- Gastroretention
- Colon targeting
- Solubility enhancement
- Permeability enhancement
- CYP3A4 or P-gp inhibition

An ideal study for serious consideration using the PK_{Plus} study approach is a traditional absolute oral bioavailability study. Normally, absolute oral bioavailability is measured in a two-way crossover design study comparing an oral immediate-release dosage form with intravenous administration as a reference. However, by adding one or

more targeted drug delivery arms to key gastrointestinal segments, information on the regional absorption of the drug can also be obtained from the same study (Martin *et al.*, 2003). Depending upon exact study requirements, the size of subject group taken forward to the regional absorption phase can also be set according to budgetary constraints. A similar approach can be applied to any PK study in the development plan.

Conclusion

Bioavailability studies are essential to drug development and form an integral part of the registration dossier. However, routine bioavailability studies do not provide a complete picture of a drug's biopharmaceutical properties. Until recently, there has only been a limited understanding of what actually controls human drug absorption. Undertaking regional absorption studies with engineering-based drug delivery capsules, such as Enterion™, provides a detailed understanding of the absorption of a drug at specific regions of the GI tract. By combining bioavailability studies with human drug absorption legs in the same study, it is possible to characterise the fundamental *in vivo* performance attributes of a drug in healthy volunteers and provide a reliable and cost-effective 'route map' for developing new drugs with complex pharmacokinetic properties.

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Mel Hemamda
Tel: +44 (0) 1865 784 177
Fax: +44 (0) 1865 784 178
E-mail: mel.hemamda@pharmaventures.com